REMARKS AND ARGUMENTS

II. Interview Summary

Applicants' representative would like to thank the Examiner for an interview on March 5, 2009, during which the pending claims and outstanding rejections were discussed. Specifically, the Applicants' representative discussed with the Examiner the issue of entitlement to priority from GB9024503.6 which removes *Bass et al.* as prior art. Applicants also discussed several distinctions between the present application and *Ladner et al.*, U.S. Patent No. 5,223,409, and possible claim amendments to further distinguish the presently claimed invention from *Ladner et al.*

III Preliminary Remarks

Support for the amendment to claim 1 "immunoglobulin domain" is found *inter alia* on page 11, line 8 of GB9024503.6 from which this application claims priority and in the application as filed.

IV. Priority

On page 2 of the office action, the Applicants were asked to clarify whether U.S. Patent No. 5, 969,108 is a 35 U.S.C. § 371 (national stage) of PCT/GB92/00883. In fact, the '108 patent is **not** a national stage of PCT/GB92/00883) but rather **it is the national stage of PCT/GB91/01134**.

On page 3 of the office action, the Examiner alleged that the claims were not entitled to priority from GB90245036 because it did not describe the contents of the phagemid. However, the Applicants respectfully submit that the present claims are fully entitled to priority entitlement from at least as early as November 12, 1990, the filing date of GB9024503.6 from which the present application claims priority. However, as was discussed in detail during the interview

with the Examiner, UK 9024503.6 at page 25 discloses a plasmid containing a single stranded phage replication origin which is by definition a phagemid such as pUC119, a phagemid in which the only nucleotide sequence derived from a filamentous phage is a phage origin of replication . (*See* Exhibit A depicting pUC119).

The following table also illustrates disclosure providing basis for the present claims in both the application as filed and Priority 3 GB9024503.6 filed November 12, 1990.

Claim	**PCT APPLICATION AS FILED**	**US APPLICATION AS FILED**	**THIRD PRIORITY DOCUMENT NOV. 12, 1990**
Claim 1	Page 17, lines 44-50, along with the paragraph bridging pages 21 and 22, also page 21, lines 7-10, for the rgdp being filamentous bacteriophage, also the experimental examples, paragraph [0020], Example 24, Figure 26.	Page 37, lines 10-17, along with page 45, lines 12-26, also page 43, line 26, to page 44, line 1, for the rgdp being filamentous bacteriophage, also the experimental examples, the paragraph spanning pages 11 and 12, Example 24, Figure 26A. Page 73, Figure 26A.	Page 10, lines 16-20, along with the paragraph bridging pages 11 and 12, also page 10, lines 35-36, for the virus being filamentous bacteriophage, and the experimental examples, page 25, lines 7-14. plasmid containing a single stranded phage replication origin (phagemid) such as pUC119 immunoglobulin domain, page 11, line 8
Claim 2	Page 17, line 52 (the first optional additional step); also paragraph bridging pages 21-22.	Page 37, lines 18-19 (the first optional additional step); also page 45, lines 12-26.	Page 10, line 22 (the first optional additional step); also first paragraph of page 12.
Claim 3	Page 18, line 1 (the second optional additional step).	Page 37, line 19 (the second optional additional step).	Page 10, lines 22-23 (the second optional additional step.)
Claim 4	Page 18, lines 1-4 (the third optional additional step), along with page 22,	Page 37, lines 20-22 (the third optional additional step), along	Page 10, lines 23-25 (the third optional additional step), along

	lines 21-24.	with page 46, lines 14-17.	with, for example, page 1, lines 7-9, and page 16, lines 10-12.
Claim 5	Page 17, line 31; page 23, lines 33-35.	Page 36, lines 21-22; page 49, lines 1-3.	

To summarize, the present claims are fully entitled to the priority date of at least November 12, 1990 for its disclosure of phagemids as presently claimed.

IV. Patentability Arguments

A. The Claim Rejections Under 35 USC §102(e) Should Be Withdrawn

1. *Ladner et al.*

Claims 1-5 continue to stand rejected allegedly as being anticipated by *Ladner et al.* U.S. Patent 5,223,409 (*Ladner et al.*). Specifically, the Examiner stated that *Ladner et al.* anticipate the instant claim 1 because it teaches methods of displaying binding proteins on the surface of filamentous bacteriophage via nucleic acid sequences including gIII and screening for target molecule binding wherein phagemids and helper phage may be utilized pointing to the abstract; columns 1, 4-12, 15-105, Examples I-XVI; and claims 1-66 of *Ladner et al.*

The Examiner also stated that *Ladner et al.* anticipate claim 2 because it teaches separating bacteriophage expressing binding proteins from the target molecules in columns 10-12, and 93-98. With respect to claim 3 it is stated that it is anticipated because it teaches recovering of separated bacteriophage in columns 10-12, 98-99. As to claim 4 it is alleged anticipated because *Ladner* et al. teach expressing the binding protein in another expression system including bacterial spores, and artificial methods, etc. in columns 8, 10, 50-77. Finally, with respect to claim 5, the Examiner alleged that *Ladner et al.* teach utilizing the methods to express antibodies including the Fc portion in columns 15-16.

In response, the Applicants reiterate below, previous arguments which distinguish the present invention from *Ladner*. In addition, the Applicants are amending the claims herewith to further distinguish the present invention from Ladner *et al.* More specifically, the claims now recite that the displayed binding molecules comprise a folded functional immunoglobulin domain that the phagemid encodes a mature gene III protein, and that the only nucleotide sequences derived from a filamentous phage in the phagemid are an origin of replication and a mature gene III protein.

Ladner et al. fails to disclose a phagemid in which the only nucleotide sequences derived from filamentous are an origin of replication and a nucleic acid encoding a mature gene III protein. *Ladner et al* fails to disclose a display of a folded functional immunoglobulin domain , its example limited to the display of BPTI which is 58 amino acids in length.

To reiterate prior arguments which in addition to the foregoing also distinguish the present invention from *Ladner et al.*, the Applicants respectfully traverse the rejections because *Ladner et al.'s* stated concern is that if a helper phage (required by the present claims) is used there will be recombination between different DNA's encoding the displayed molecules as is called for by the present claims and thus that the genotype/phenotype connection would be lost. This would apply whatever the population source, from controlled mutagenesis or otherwise. When *Ladner et al.* says that "Phagemids may be entirely suitable for developing a gene that causes an IPBD to appear on the surface of phage-like genetic packages" this refers to making a phagemid with the full genome of M13, as discussed in detail in Applicants' previous response.

With respect to this disclosure in *Ladner et al.* did not use Bluescript K/S that is mentioned in column 76 but rather teaches the shortcomings of that phagemid and does not teach

the combination of that phagemid with a nucleic acid encoding and a mature gene III protein, therefore, cannot properly cannot anticipate the present invention.

Still further, the office action alleges that *Ladner et al.* discloses employing pGEM® -3Zf in column 106. Specifically, the Office Action states:

> "the construct comprising gIII-binding domain would be inserted into the multiple cloning site for phage display (i.e. plasmid would then contain only ori and gIII of filamentous bacteriophage; please refer to columns 53-59, section IV.B)"

However, the actual disclosure of *Ladner et al.* does not describe that at all. In relation to column 106 of *Ladner et al.*, pGEM® -3Zf is the **STARTING MATERIAL** for the construction of a vector that explicitly according to *Ladner et al.* employs gene VIII coat protein (not gene III) as fusion partner. The present invention as claimed employs a mature gene III capsid protein not the gene VIII coat protein and thus it is novel and not anticipated by the vector construct described in column 106 of *Ladner et al.* for this reason in itself. Furthermore, it is explicit in column 106 of *Ladner et al.* that the signal peptide employed is a filamentous bacteriophage gene VIII signal peptide, the construct created being:

viii-signal-sequence::bpti::mature-viii-coat-protein

The gene VIII signal peptide is a nucleotide sequence derived from filamentous bacteriophage that is other than an origin of replication and a nucleotide sequence encoding a mature gene III capsid protein in that the signal peptide is not a component of the viral capsid protein, being cleaved away. The presence of such an additional filamentous bacteriophage component in addition to the only two permitted in the claim as currently amended prevents *Ladner et al.* from anticipating the present invention.

Applicants note that column 111 and Figure 5 of *Ladner et al.* discuss construction of an alternative M13-MB51 in which M13 gene III signal peptide is fused to the BPTI :mature:VIII coat protein. Again, there is no gene III capsid protein employed, as required by the present claims, and further the use of gene III signal peptide puts the subject-matter outside of the scope of the present claims. Other filamentous bacteriophage nucleotide sequences are also present. The constructed plasmid MB51 does not contain only origin of replication and mature gIII of filamentous bacteriophage.

In relation to columns 53-59, section IV. B, as cited in the Office Action, these columns make no mention of phagemid at all. Furthermore, column 56 at the top refers to use of "RF M13" and says the "M13 genome is expandable". As has been previously explained, RF (replicable form) genome contains all the phage genes (not just an origin of replication and a nucleotide sequence encoding a mature gene III capsid protein) and this section is discussing including a complete phage genome and adding in genes.

Further, *Ladner* does not disclose a display of a folded functional immunoglobulin. *Ladner* is concerned with methods that involve use of an "IPBD" – "Initial Potential Binding Domain" – to search for binding proteins with binding properties relative to the target that are superior to the initial binding properties. See, *e.g., Ladner,* column 11, and throughout the specification.

Column 16 of *Ladner* defines "binding protein" (BP) and "initial potential binding domain" (IPBD), which is what is to be displayed and subject to variegation:

> When a domain of a protein is primarily responsible for the protein's ability to specifically bind a chosen target, it is referred to herein as a "binding domain" (BD). A preliminary operation is to engineer the appearance of a stable protein domain, denoted as an "initial potential domain" (IPBD), on the surface of a genetic package.

See also, column 18

IPBD	Initial Potential Binding Domain, *e.g.*, BPTI
PBD	Potential Binding Domain, *e.g.*, a derivative of BPTI
SBD	Successful Binding Domain, *e.g.*, a derivative of BPTI Selected for binding to a target
PPBD	Parental Potential Binding Domain, *i.e.*, an IPBD or an SBD from a previous selection.

Column 20 of *Ladner* discusses the selection of IPBD:

> Preferably, the IPBD is no larger than necessary because small SBDs (for example, less than 30 amino acids) can be chemically synthesized and because it is easier to arrange restriction sites in smaller amino-acid sequences. For PBDs smaller than about 40 residues, an added advantage is that the entire variegated pbd gene can be synthesized in one piece. In that case, we need arrange only suitable restriction sites in the osp gene. A smaller protein minimizes the metabolic strain on the GP or the host of the GP. The IPBD is preferably smaller than about 200 residues. The IPBD must also be large enough to have acceptable binding affinity and specificity. For an IPBD lacking covalent crosslinks, such disulfide bonds, the IPBD is preferably at least 40 residues; it may be as small as six residues if it contains a crosslink. These small, crosslinked IPBDs, known as "mini-proteins", are discussed in more detail later in this section.

There is emphasis on the IPBD being " no larger than necessary" with small domains being preferred. There is an explicit statement "The IPBD is preferably smaller than about 200 residues." This paragraph is further qualified by the following paragraph that describes various potential properties to be taken into account:

> Some candidate IPBDs, which meet the conditions set forth above, will be more suitable than others. Information about candidate IPBDs that will be used to judge the suitability of the IPBD includes: 1) a 3D structure (knowledge strongly preferred), 2) one or more sequences homologous to the IPBD (the more homologous sequences known, the better), 3) the pI of the IPBD (knowledge desirable when target is highly charged), 4) the stability and solubility as a function of temperature, pH and ionic strength (preferably known to be stable over a wide range and soluble in conditions of intended use), 5) ability to bind metal ions such as

> CA^{++} or Mg^{++} (knowledge preferred; binding *per se*, no preference), 6) enzymatic activities, if any (knowledge preferred, activity per se has uses but may cause problems), 7) binding properties, if any (knowledge preferred, specific binding also preferred), 8) availability of a molecule having specific and strong affinity ($K_d<10^{-11}M$) for the IPBD (preferred), 9) availability of a molecule having specific and medium affinity ($10^{-8}M<K_d<10^{-6}M$) for the IPBD (preferred), 10) the sequence of a mutant of IPBD that does not bind to the affinity molecule(s) (preferred), and 11) absorption spectrum in visible, UV, NMR, etc., (characteristic absorption preferred).

Thus, while the generic disclosure within *Ladner* teaches a preference for small, stable protein domains (but does entertain the possibility of larger ones), there is no explicit demonstration of display of large folded functional immunoglobulin domains on the surface of filamentous bacteriophage (as a GP).

In view of the amendments to the claims differences between the *Ladner et al.* disclosure and the subject-matter as presently claimed and as discussed above, Applicants respectfully submit that *Ladner et al.* cannot properly anticipate any of the pending claims as a matter of law and, therefore, the rejections of the claims over *Ladner et al.* may be properly withdrawn and withdrawal is requested.

2. Bass et al.

Claims 1-3 and 5 continue to stand rejected under 35 U.S.C. 102(e) allegedly as being anticipated by U.S. Patent 5,688,666 to inventor *Bass* et al. (*Bass et al.)*

Paragraph 13 of the Office Action states that *Bass et al* teach methods for selecting novel proteins having altered binding properties comprising producing a library of filamentous bacteriophage, surface displaying a library of mammalian proteins including antibodies wherein each filamentous bacteriophage contains a phagemid comprising nucleic acid encoding the protein. It is further stated that in *Bass et al.*, the only nucleic acid sequences derived from

filamentous bacteriophage consists of ori and gene III wherein a helper phage is utilized to package the phagemid. However, as explained in more detail below the *Bass et al* disclosure on which the rejection is based, was added in a continuation-in-part application with a priority date after the disclosure of the above identified patent application. Therefore, *Bass et al* cannot be properly cited as a prior art reference against the pending claims for its allegedly anticipating disclosure.

Anticipation by *Bass et al* is alleged based on subject-matter in *Bass et al* said to relate to selection of novel proteins employing a library of filamentous bacteriophage surface display a library of growth hormone variants or other mammalian proteins including antibodies. As discussed in Applicants' previous response, none of the subject-matter cited is entitled to a date earlier than December 3, 1990 at best, certainly no date earlier than any of the first three priority dates for the present application (set out below).

The present application claims the benefit of the following five priority applications:

Priority 1	GB 9015198.6	filed July 10, 1990
Priority 2	GB 9022845.3	filed October 19, 1990
Priority 3	GB 9024503.6	filed November 12, 1990
Priority 4	GB 9104744.9	filed March 6, 1991
Priority 5	GB 9110549.4	filed May 15, 1991.

The present application also has a PCT filing date of July 10, 1991.

Of the applications from which *Bass et al* claims benefit, only 264,611 filed October 28, 1988 is earlier than all of the priority applications for the present application. Original *Bass* application (264,611) filed October 28, 1988 contains no disclosure relating to display of any protein on the surface of filamentous bacteriophage.

The next application from which *Bass et al* claims benefit is 621,667 filed December 3, 1990, and this was a continuation-in-part adding some disclosure to the contents of 264,611 filed October 28, 1988. However, December 3, 1990 is after the filing of the first three priority applications for the present application. For subject-matter in the present application entitled to at least the priority of Priority 3 GB 9024503.6 filed November 12, 1990, the contents of *Bass* 621,667 filed December 3, 1990 are not prior art. Furthermore, any subject-matter filed first by *Bass* in 682,400 filed April 10, 1991 is not prior art to subject-matter in the present application entitled to at least the priority of Priority 4 GB 9104744.9 filed March 6, 1991.

The present claims are fully entitled to priority entitlement from at least Priority 3 GB9024503.6 filed November 12, 1990. Page 3 of the Office Action states that UK 9024503.6 filed on November 12, 1990 does not disclose a phagemid. However, as was discussed in detail during the interview with the Examiner, UK 9024503.6 discloses pUC119 at page 26. (*See* Exhibit A depicting pUC119). This is a plasmid (phagemid) in which the only nucleotide sequences derived from a filamentous bacteriophage are an origin of replication and a nucleotide sequence encoding a gene III protein.

The following table illustrates disclosure providing basis for the present claims in both the application as filed and Priority 3 GB9024503.6 filed November 12, 1990.

Claim	PCT APPLICATION AS FILED	US APPLICATION AS FILED	THIRD PRIORITY DOCUMENT NOV. 12, 1990
Claim 1	Page 17, lines 44-50, along with the paragraph bridging pages 21 and 22, also page 21, lines 7-10, for the rgdp being filamentous bacteriophage, also the experimental examples, paragraph [0020], Example 24, Figure 26.	Page 37, lines 10-17, along with page 45, lines 12-26, also page 43, line 26, to page 44, line 1, for the rgdp being filamentous bacteriophage, also the experimental examples, the paragraph spanning pages 11 and 12, Example 24, Figure 26A. Page 73, Figure 26A.	Page 10, lines 16-20, along with the paragraph bridging pages 11 and 12, also page 10, lines 35-36, for the virus being filamentous bacteriophage, and the experimental examples, page 25, lines 7-14. plasmid containing a single stranded phage replication origin (phagemid) such as pUC119 immunoglobulin domain page 11, line 8
Claim 2	Page 17, line 52 (the first optional additional step); also paragraph bridging pages 21-22.	Page 37, lines 18-19 (the first optional additional step); also page 45, lines 12-26.	Page 10, line 22 (the first optional additional step); also first paragraph of page 12.
Claim 3	Page 18, line 1 (the second optional additional step).	Page 37, line 19 (the second optional additional step).	Page 10, lines 22-23 (the second optional additional step.)
Claim 4	Page 18, lines 1-4 (the third optional additional step), along with page 22, lines 21-24.	Page 37, lines 20-22 (the third optional additional step), along with page 46, lines 14-17.	Page 10, lines 23-25 (the third optional additional step), along with, for example, page 1, lines 7-9, and page 16, lines 10-12.
Claim 5	Page 17, line 31; page 23, lines 33-35.	Page 36, lines 21-22; page 49, lines 1-3.	

To summarize, the present claims are fully entitled to the priority date of at least November 12, 1990 and *Bass* is only entitled to December 3, 1990. In view of the above-discussed priority dates of the *Bass et al* disclosure as compared to the priority dates of the above-identified patent application, *Bass et al* cannot properly be cited as prior art against the

pending claims and therefore, the rejection of claims 1-3 and 5 under 35 U.S.C. 102(e) over *Bass et al* may be properly withdrawn and withdrawal is respectfully requested.

B. The Claim Rejections Under 35 USC §103(a) Should Be Withdrawn

Claims 1-5 continue to stand rejected under 35 USC §103(a) allegedly as being obvious over *Bass et al* in view of U.S. Patent 5,534,617 to inventor Cunningham et al. ("*Cunningham et al.")* As discussed in Section A2 of this response, the *Bass et al* disclosure is not a proper prior art reference to the pending claims because it is filing date is after the priority date to which the present application is entitled. Because, *Bass et al* is not prior art with respect to the present application, it cannot render the pending claims obvious as a matter of law and therefore, the rejection over *Bass et al* in view of *Cunningham et al* under 35 USC §103(a) should be withdrawn and withdrawal is respectfully requested.

CONCLUSION

Applicants believe that the application is in good and proper order for allowance and such allowance is respectfully solicited. The Examiner is hereby respectfully invited to contact the undersigned attorney at the number listed below with any questions, comments or suggestions relating to this application. Should any additional fees be required for further prosecution of the above-identified patent application, the Commissioner is authorized to deduct any such fees from Howrey LLP Deposit Account No. 08-3038, referencing the above-identified docket number.

Respectfully submitted,
HOWREY LLP

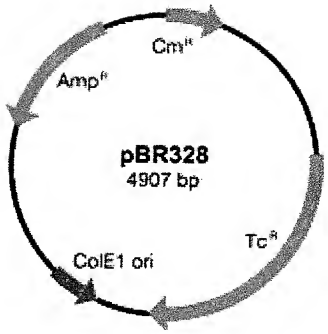
By: /David W. Clough/
David W. Clough, Ph.D.
Registration No.: 36,107
Telephone: (312) 595-1408
Customer ID No. 22930

Dated: May 4, 2009

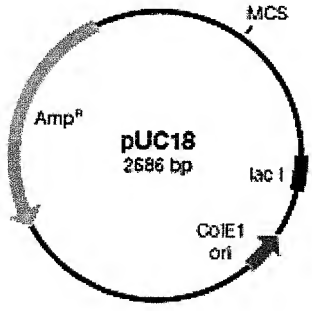
HOWREY LLP
ATTN: Docketing Department
2941 Fairview Park Drive, Suite 200
Falls Church, VA 22042-2924
Telephone No.: (703) 663-3600
Facsimile No.: (703) 336-6950

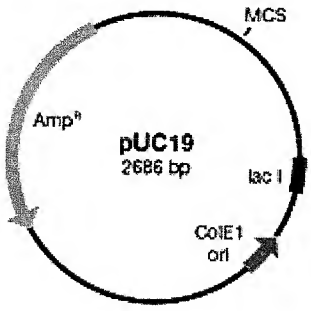
EXHIBIT A

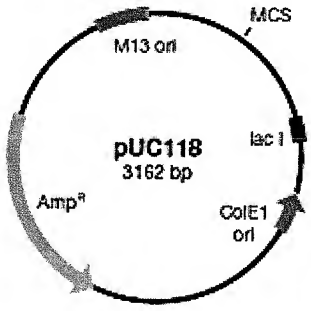
cloning vector. This vector, derived from pBR325, has the *bom* site (basis of mobility) deleted and therefore is non-mobilizable; this makes pBR328 suitable where more stringent biological containment is required. This deletion also creates extra unique cloning sites in the chloramphenicol acetyltransferase gene: *Pvu* II, *BspM* II and *Bal* I.



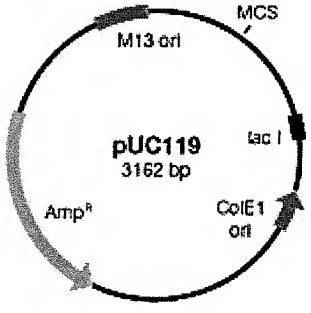
Vector	Resistance	Origin	Speciality
pBR322	Tc, Amp	ColE1	reading frame shift gives Amp^R , Tc^S transformants
pBR325	Tc, Amp, Cm	ColE1	Cm resistant pBR322
pBR328	Tc, Amp, Cm	ColE1	non-mobilizable pBR325
pACYC184	Tc,Cm	p15A1	double-transformants with ColE1 vectors
pAT153	Tc, Amp	ColE1	non-mobilizable; higher copy than pBR322
pUC18	Amp	ColE1	MCS within lacZ: blue/white selection
pUC118	Amp	ColE1	M13 origin for ssDNA production
pUC19	Amp	ColE1	MCS within lacZ:blue/white selection
pUC119	Amp	ColE1	M13 origin for ssDNA production







pUC18/19 and pUC118/119:



The plasmids have a multiple cloning site within the lacZ alpha-fragment. Inserts cloned into this site disrupt beta - galactosidase activity and give rise to white colonies on X-Gal/IPTG plates. The plasmids encode resistance to ampicillin. Foreign DNA inserted in-frame with the lac Z gene will be expressed as a fusion protein (containing a portion of the beta-galactosidase) under control of the lac